Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 39-51 are pending in this application and are rejected on various grounds. Claims 39-43 and 47-48 have been canceled without prejudice or disclaimer. Claims 44-47 and 49-50 have been amended for proper claim dependencies, to remove references to "Figures" in the claims for clarity. No new matter has been added due to these amendments. The rejections to the presently pending claims are respectfully traversed.

Formal matters

1. The title of the invention has been amended to accurately describe the claimed invention.

2. Claims 45-46 and 49 have been amended with the previously lacking "period" following the claim number.

3. The disclosure was objected to for reciting the incorrect ATCC address. The foregoing amendments to the specification correct the address and further, delete all embedded hyperlinks in order to keep this application compliant with USPTO's rules. Applicants believe that this amendment should overcome the present objections.

Information Disclosure Statement

Applicants submit an IDS separately enlisting references recited in the Blast report filed 3/25/2002 in order to be compliant with 37 C.F.R. § 1.98(a)(1). Consideration of this Information Disclosure Statement is respectfully requested.

Priority

The Examiner asserts that Applicants are only entitled to the priority of the instant Application, dated July 16, 2001, since "the claimed subject matter does not have a substantial asserted utility or a well established utility." Without admitting that specific recognition of utility is necessary for priority entitlement, as will be apparent from the rest of the response, Applicants rely on the gene amplification assay (Example 92) for support of patentable utility. This data was first disclosed in the International application PCT/US/00/03565 (P2931R1), filed on 11

February, 2000, priority to which is claimed in the present application. Accordingly, Applicants believe that the effective filing date of this application is at least **February 11, 2000.**

Claim Rejections – 35 U.S.C. § 112, second paragraph

Claims 39-58 were rejected under 35 U.S.C. §112, second paragraph for being indefinite. The Examiner says that the claims recite "the extracellular domain" in part (c) and (d) and "an extracellular domain...lacking its associated signal sequence."

Applicants have canceled claims 47-48, references to "extracellular domain" and parts (c) and (d) in pending claims for clarity. Accordingly, Applicants submit that the claims are now definite and respectfully request that this rejection be withdrawn.

Claim Rejections – 35 U.S.C. § 112, first paragraph

Claims 39-58 are rejected under 35 U.S.C. §112, first paragraph allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

Claims 39-43, 47-48 have been canceled and hence rejections to these claims are moot. As discussed below, Applicants rely on the gene amplification assay for patentable utility of PRO304 nucleic acids and corresponding polypeptides, thus entitling the present application to an effective filing date of February 11, 2000.

Gene amplification is an essential mechanism for oncogene activation. It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis. As described in Example 92 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9 (pages 229-234 of the specification), including primary lung and colon cancers of the type and stage indicated in Table 8 (page 227). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 222, lines 34-36). Gene amplification was monitored using real-time quantitative TaqMan™ PCR. The gene amplification results are set forth in Table 9. As explained in the passage bridging pages 222 and 223, the results of TaqMan™ PCR are reported in ΔCt units. One ΔCt unit corresponds to one

PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold, etc. amplification. PRO304 showed approximately 2.00-3.204 fold amplification in 7 primary lung tumors, figures which are way above figures considered significant. Hence, these data clearly support a role for PRO304 nucleic acids as a lung tumor marker.

Regarding the Examiner's rejection of the PRO304 polypeptide as a diagnostic agent based on the lack of an explanation for aneuploidy, Applicants have enclosed a Declaration by Dr. Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the present application. As Dr. Ashkenazi explains:

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

The Declaration by Dr. Avi Ashkenazi further explains:

> If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

In further support of the fact that, as a rule, there is expected to be a correlation between gene amplification and protein overexpression, please find enclosed an article by Celis et al., FEBS Letters 480: pages 2-16, (2000). Celis et al. report on recent studies on microarray and proteomic data and studies that compare transcript and protein expression levels, for example, in bladder cancer. Celis et al. report on page 13, column 1, paragraph 4:

> Recently, Orntoft et al., (manuscript in preparation) carried out a microarray and proteomic study of bladder cancer in which they compared the transcript and protein expression levels of pairs of non-invasive and invasive low grade fresh TCCs. Even though they could only compare the levels of about 40 well-resolved and focused abundant proteins, **it was clear that in most cases there was a good correlation between transcript and protein levels** (emphasis added). Only in a few cases they found discrepancies, and in some of those instances they could eliminate the possibility that this was due to messenger stability, post-transcriptional splicing, post-translational

modifications, protein focusing problems, degradation, as well as the choice of methods used to assess protein expression levels (staining versus radiolabelling).

This review paper clearly indicates that, it is more likely than not that there is a correlation between mRNA and protein levels, and therefore, our assertion that PRO304 protein may be used as a diagnostic agent clearly meets the legal standard. The Examiner will appreciate that absolute predictability is not a requirement.

Thus, Applicants have demonstrated gene amplification data that clearly support a role for PRO304 nucleic acid and polypeptides as lung tumor markers. Accordingly, the present 35 U.S.C. §101/ 112, first paragraph utility rejections should be withdrawn.

Claim Rejections - 35 USC § 112, first paragraph

Claims 39-44, 47-48, 50- 51 are rejected under 35 U.S.C. §112, first paragraph for allegedly not being described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time of filing.

In view of the cancellation of claims 39-43 and 47-48, rejections to these claims are moot. Amended Claim 44 and its dependent claims are clearly described in the specification. Applicants submit that the skilled artisan would accept that Applicants had possession of the presently claimed subject matter at the time of filing.

Hence, this rejection should be withdrawn.

Deposit requirement

Claims 39-44 and 49-51 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter not described in the specification in such a way as to enable one skilled in the art how to make or use the invention.

Applicants submit that the present amendments to the specification have incorporated the requisite assurances that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent." Thus, this rejection is obviated.

Rejections over Prior art

1) Claims 39-43 and 50-51 are rejected under 35 U.S.C. §102(e) as being anticipated by Lobel et al., USPN 6302685 (October 2001).

2) Claims 39-43 are rejected under 35 U.S.C. §102(b) as being anticipated by Sleat et al., Science 277: 1802-05, (September 1997).

3) Claims 39-43 and 50-51 are rejected under 35 U.S.C. §102(b) and §102(e) as being anticipated by Jacobs et al., USPN 5831056 (November 1998).

The above rejections are moot in view of the cancellations of claims 39-43 and change of dependency of claims 50-51 onto non-rejected claim 44. Thus, these rejections should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C35). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

/

Date: April 16, 2004

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